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Transfer of dexamphetamine into breast milk during treatment for attention deficit hyperactivity disorder

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What is already known about this subject

- There are presently no published data on dexamphetamine transfer into breast milk or on its effects in the breast-fed infant.

What this study adds

- We have provided quantitative data on the absolute and relative infant doses of dexamphetamine for the breast-fed infant.
- We have also documented a lack of overt adverse effects in breast-fed infants despite measurable dexamphetamine concentrations in the infants' plasma.
- Hence we now make recommendations for infant safety and monitoring when mothers taking the drug wish to breastfeed.

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Aims
To investigate dexamphetamine transfer into milk, infant doses and effects in the breast-fed infant.

Methods
Four women taking dexamphetamine, and their infants were studied.

Results
The median maternal dexamphetamine dose was 18 mg day^{-1} (range 15–45 mg day^{-1}). Median (interquartile range) descriptors were 3.3 (2.2–4.8) for milk/plasma ratio, 21 μg kg^{-1} day^{-1} (11–39) for absolute infant dose and 5.7% (4–10.6%) for relative infant dose. No adverse effects were seen. In three infants tested, dexamphetamine in plasma was undetected in one (limit of detection 1 μg l^{-1}) and present at 18 μg l^{-1} and 2 μg l^{-1} in the other two.

Conclusion
Dexamphetamine readily transfers into milk. The relative infant dose was <10% and within a range that is generally accepted as being 'safe' in the short term.

Introduction

Dexamphetamine (*S*-(+)-isomer of amphetamine) is a common pharmacotherapy for attention deficit disorder and attention deficit hyperactivity disorder (ADHD) in children and adolescents [1]. These disorders are now recognized as carrying through into adult life and thus dexamphetamine is sometimes taken by women of childbearing age [2]. This raises the question of the safety of breastfeeding during dexamphetamine treatment. In a single case report, *rac*-amphetamine (15 mg oral dose; 50 : 50 mixture of *S*-(+)- and *R*-(–)-isomers) was shown to concentrate in breast milk [milk to plasma ratio (M/P) ranged from 2.8 to 7.5], with resulting milk concentrations of 55–138 μg l^{-1} [3]. However, the extent of transfer of dexamphetamine into milk, or the safety of breastfeeding whilst taking the drug, has not been established. The American Academy of Pediatrics considers amphetamines to be contraindicated during breastfeeding [4] and we and others have counselled against their use largely on the basis of their theoretical potential for causing adverse effects in the breast-fed infant [5, 6]. The aim of the present study was therefore to provide quantitative evidence of the transfer of dexamphetamine into milk, the extent of infant exposure, and to assess any unwanted effects in the breast-fed infant.

Materials and methods

Patients

Four breastfeeding women who were being treated with dexamphetamine (Dexamphetamine sulphate 5 mg tablets; Sigma Pharmaceuticals Pty Ltd, Croydon, Australia) for ADHD gave written informed consent to their participation and were enrolled in the study.

Study protocol and data collection

The study was approved by the Ethics Committee of the Women's and Children's Health Service, Subiaco, Australia. The mothers were admitted to the research ward at 08.00 h and took their first dose of the day shortly thereafter. In two cases, venous blood samples (5 ml each, lithium heparin tube) were taken just before the first morning dose of dexamphetamine, and at 2, 4 and 6, 7 or 8 and 24 h (one only at 24 h) postdose. In the remaining two cases, a single blood sample was taken 3–4 h after the first dose. The mothers collected milk samples (8 ml each, usually an equal mixture of fore- and hind-milk) by hand expression or manual breast pump just before the morning dose, and again every time their infant fed during the next 24 h (usually six to eight feeds; timing can be seen in Figure 1).

Infant health and well-being were evaluated by enquiry of the mother and the referring physician. A full clinical examination, including a Denver development assessment [7, 8], was able to be carried out by a specialist neonatologist in two of the cases only.

Materials

D-amphetamine sulphate and phentermine hydrochloride were obtained from Sigma-Aldrich Corporation (Castle Hill, Australia). All other solvents and chemicals were of high-performance liquid chromatographic or analytical grade.

High-performance liquid chromatography

Dexamphetamine in plasma and milk was measured using a previously described method for analysis of fluvoxamine [9], with the following minor changes: phentermine HCl as the internal standard, 5% CH_3CN in 45 mM phosphate buffer (pH 3) as the mobile phase. Relative standard deviations for the assay measured at 10 and 400 μg l^{-1} were: milk intraday 11% and 5.8%, respectively, and milk interday 11.4% and 7.6%, respectively; plasma intraday 5.9% and 1.9%, respectively, and plasma interday 9.5 and 3.3%, respectively. The limit of detection was 1 μg l^{-1} for both matrices.

Data analysis

Areas under milk concentration–time curves ($AUC_{0,t}$) were calculated using the mixed log-linear trapezoidal rule as appropriate [10]. The average drug concentration in milk was calculated as $C_{av} = (AUC_{0,t})/t$, where t = the period over which samples were collected (usually 24 h). AUC measurements were also made for plasma concentration–time data in two of the patients (0–24 h for A and 0–6 h for B). M/P was calculated from the respective AUC data for patients A and B and from single paired concentration measurements in milk and plasma for patients C and D.

The absolute infant dose (μg kg^{-1} day^{-1}) was calculated as the product of C_{av} and an average infant milk intake of 0.15 l kg^{-1} day^{-1} [11]. The relative infant dose was calculated as absolute infant dose/maternal dose (μg kg^{-1} day^{-1}) and expressed as a percentage [5]. Maximum concentrations (C_{max}) of drug in milk were interpolated from the primary data. Statistical analysis of data was performed using SigmaStat Ver 3.1 (SPSS Inc., Chicago, IL, USA). Data have been summarized as mean (range) or median [range, or interquartile range (IQR)], as appropriate.

Results

The women had a mean age (range) of 35 years (27–40), their mean body weight was 67 kg (58–73) and they had

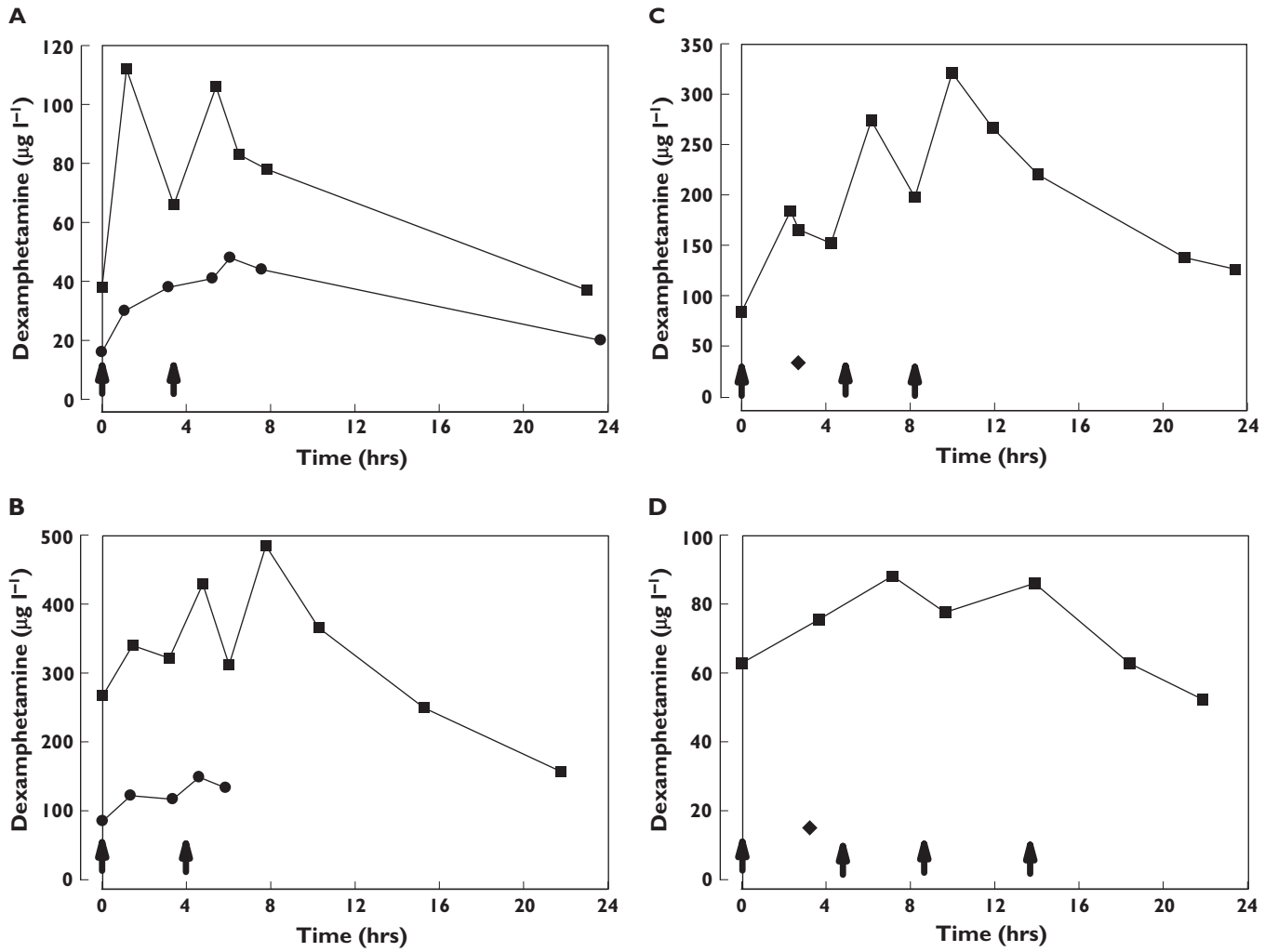

Figure 1

(A–D) Dexamphetamine concentration–time plots in milk (■) and plasma (●) for patients A to D. Doses were taken orally at the times shown by the arrows as follows: patient A, 10 mg and then 5 mg; patient B, 20 mg and then 25 mg; patient C, 3 × 5 mg; and patient D, 4 × 5 mg. Measured concentrations of dexamphetamine in infant plasma are shown by the (◆) symbol in C and D

been taking a median (range) dexamphetamine dose of 18 mg day^{-1} (15–45) for a median 48 months (2–60). Their infants (three female and one male) were a mean (range) age of 5.5 months (3.3–10) on the study day. They weighed 3.4 kg (3.1–4) at birth and 6.5 kg (5.2–8.2) on the study day and had been breast fed since birth. The median single daily dose of dexamphetamine taken by the women was 18 mg (range 15–45), therapy had commenced a median of 48 months prior to the study day and they were therefore considered to be at steady state. The women all took split doses (two to four portions) over the first half of the day (see Figure 1 for dose and timing details). The infants had achieved acceptable weight for age milestones (between 10th and 75th percentiles) at the time of study. For all four infants, the mothers and/or their referring physicians reported 'normal' progress. Paediatric assessments done for two of them did not reveal any adverse findings and Denver developmental ages (as percentage chronological age) were 100% (infant of C) and 117% (infant of D).

Milk and plasma concentration–time profiles for the women are shown in Figure 1, while details of drug concentration in milk and plasma and infant dose and exposure are summarized in Table 1. Milk C_{max} values were highly dependent on dose time (Figure 1). Median values for M/P, absolute infant dose and relative infant dose were 3.3, 21 μg kg^{-1} day^{-1} and 5.7%, respectively. Three of the women permitted a blood sample to be taken from their infants. Dexamphetamine in plasma was undetected in one infant (D), and was present in the

Table 1
Dexamphetamine concentrations in milk and plasma, milk to plasma (M/P) values, maternal and infant doses and infant plasma concentrations

Mother–infant pair	Milk C_{max} (μg l^{-1})	Milk C_{av} (μg l^{-1})	Plasma C_{single} or C_{av} (μg l^{-1})	M/P*	Maternal dose (μg kg^{-1} day^{-1})	Absolute infant dose (μg kg^{-1} day^{-1})	Relative infant dose (%)	Infant plasma concentration (μg l^{-1})
A	112	66	34	1.9	259	10	3.9	2
B	486	313	131	2.4	643	47	7.3	18
C	325	206	41	4.2	224	31	13.8	ND
D	86	73	14	5.3	274	11	4.0	<1
Median (IQR)	219 (99–406)	140 (70–260)	38 (24–86)	3.3 (2.2–4.8)	267 (242–459)	21 (11–39)	5.7 (4–10.6)	

**M/P calculated from AUC data for patients A and B and from single paired data for patients C and D; ND, no plasma sample available.*

other two infants at concentrations that were approximately 6% (A) and 14% (B) of the corresponding maternal plasma concentration.

Discussion

The use of psychoactive drugs during breastfeeding should be a concern to both the mothers who need drug therapy, and their prescribing physicians. It is encouraging to see that as more information on drug transfer into milk and its effects in the breast-fed infant has become available, many psychoactive drugs such as antiepileptics [12, 13] and antidepressants [14] have become accepted as being 'safe', at least for short-term use, with the proviso that there is regular careful follow-up of the infant. Dexamphetamine use in breastfeeding has two major problems. First, its membership of the amphetamine class drugs, which are recreational drugs of abuse, promotes a conservative approach in both patient and prescriber. Second, the lack of published data on its use in breastfeeding at present prohibits the rational evaluative approach that has been applied to other psychoactive compounds. The only published data of relevance to dexamphetamine milk transfer and infant exposure are of a single case where *rac*-amphetamine was studied [3]. Using the milk concentration data from this report, it can be calculated that the relative infant dose for *rac*-amphetamine would be in the range 2.5–6.2%. Our study shows that dexamphetamine readily transfers into milk with a median M/P of 3.3. This accords with the physicochemical properties of the molecule (pKa 9.9, $\log_{10}$P 1.81, plasma protein binding 16%) [15, 16] and the fact that milk pH is around 0.2 units lower than plasma [17]. Nevertheless, M/P is only a measure of transfer capability and should not be misinterpreted as a surrogate for infant dose or exposure. The milk dexamphetamine concentrations in our study were similar (per unit dose) to those reported for *rac*-amphetamine [3]. The median calculated relative infant dose for dexamphetamine was 5.7% (range 3.9–13.8%) of the weight-adjusted maternal dose and again is similar to that calculated for *rac*-amphetamine. Based on the calculated median level of exposure, one might be tempted to conclude that dexamphetamine is compatible with breastfeeding (acceptable relative infant dose <10% [11]). However, even in our small sample of four patients, there was 3.5-fold range in relative infant dose, with one value as high as 13.8%. Interestingly, in 1973 a large observational study reported no neonatal stimulation or insomnia in 103 nursing infants whose mothers were taking various doses of amphetamine [18]. Nevertheless, given the broad spectrum of cardiovascular and central nervous system effects of amphetamine [19], and the fact that two of three infants examined in our study had significant plasma concentrations of amphetamine (6 and 14% of average maternal plasma concentrations), we suggest that dexamphetamine use in breastfeeding may be acceptable only when there is reliable knowledge of the maternal dosing, and with regular clinical monitoring of the infant, including the measurement of plasma concentrations. This approach accords with the current recommendations for the use of the antiepileptic lamotrigine where infant exposure is of a similar magnitude [13]. We note that none of the four infants we studied showed any adverse effects, and while the

number is small, the findings support the cautious use of dexamphetamine during lactation. However, the medium- to long-term consequences, if any, of such exposure are unknown and each decision to breastfeed should always be made on the basis of an individual risk:benefit analysis.

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